REMARKS

Claims 1-9, 11-25, 31-33, 35 and 36 are pending in this application. Of these, claims 1, 17, 20, 23, and 31 have been amended to promote clarity and to further define the scope of the invention.

Amendment 1

Claims 1, 17, 20, 23 and 31 are amended to specify that the purified osteogenic protein is isolated from naturally-occurring sources or produced by recombinant DNA techniques. Support for this amendment appears in the specification at p. 40, lines 7-9.

This amendment is made in response to the Examiner's assertion that "not associated with other osteogenic proteins with which it is normally associated *in vivo*" introduces new matter. Office Action, ¶ 7, pp. 7-8. See also discussions below.

Amendment 2

Claim 1 is further amended to specify that the claimed device does not include a synthetic polymer matrix or a demineralized bone matrix.

In applicants' earlier responses, this claim was amended to recite "a matrix that does not comprise a synthetic polymer or demineralized bone." The Examiner states that since the claimed device comprises a matrix, that amendment fails to particularly require that the device as a whole does not include a synthetic polymer or demineralized bone. Office Action, ¶ 4, p. 3. In response to this comment, the instant amendment is made for clarification.

The amendment introduces no new matter. Applicants request

reconsideration of the pending claims in light of the above amendments and the following remarks.

Rejection Under 35 U.S.C. § 112, 1st ¶

Claims 1, 17, 20, 23 and 31 are newly rejected for lacking written support in the specification. More particularly, the Examiner contends that the claim limitation introduced in applicants' previous Response "not associated with other osteogenic proteins with which it is normally associated *in vivo*" is new matter. Office Action, ¶ 7, pp. 7-8.

Applicants disagree. Applicants' disclosure provide support for osteogenic proteins that are "isolated from naturally-occurring sources, or produced by recombinant DNA or other synthetic techniques" (p. 40, lines 7-10). A skilled person in the molecular biology art can readily understand that this passage describes the only known ways of making proteins to date – purification from natural sources, recombinant technology and chemical synthesis. Thus, the claim limitation in issue is fully commensurate in scope with the disclosure.

However, in the sole interest of expediting prosecution, applicants have amended claims 1, 17, 20, 23 and 31 to require that the purified osteogenic protein be isolated from naturally-occurring sources or produced by recombinant DNA techniques. Thus, the instant rejection can be withdrawn.

Rejection Under 35 U.S.C. § 102(e)

I

Claims 1-5, 7, 8, 9, 11, 12, 15 and 16 remain rejected as allegedly anticipated by Kuberasampath (United States Patent 5,645,591). Specifically, the Examiner states that applicants' arguments in their previous Response are not persuasive because the transitional term "comprising" does not exclude additional, unrecited elements. As such, the claimed device does not exclude a matrix that is a synthetic polymer. Office Action, p. 3, lines 4-9.

Amendment 2 discussed above addresses this issue. As amended, base claim 1 specifies that the claimed device does not include a synthetic polymer matrix. Thus, the Examiner's argument can be laid to rest.

The Examiner also asserts that Kuberasampath's device comprises collagen, and as such, anticipates claim 8. Office Action, p. 3, lines 9-12.

Applicants respectfully disagree. As discussed in applicants' *Response to August 17, 1999 Office Action* filed January 18, 1999, Kuberasampath's device contains a collagen-GAG polymer made artificially by cross-linking collagen and GAG (p. 8). That polymer is a synthetic polymer.[1] In contrast, claim 8, which depends from claim 1, requires that the claimed does not contain a synthetic polymer.

The Examiner further asserts that Kuberasampath teaches the use of recombinant osteogenic protein. Office Action, p. 3, lines 13-16. Even if this is the case, Kuberasampath still does not anticipate any of claims 1-5, 7, 8, 9, 11, 12, 15 and 16 for the above reasons. To anticipate a claim, a reference must teach every element

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1 Indeed, by arguing that the claimed devices do not exclude a synthetic polymer matrix and thus Kuberasampath anticipates these devices, the Examiner apparently agrees that Kuberasampath's matrix is synthetic.

of the claim. MPEP § 2131. Kuberasampath fails to do that.

II

Claims 1-5, 7-9, 11-13 and 31 stand newly rejected as allegedly anticipated by Tucker. The Examiner states that Tucker teaches an osteogenic protein comprising recombinant OP-1, collagen and CMC. Office Action, ¶ 10, p. 9. Applicants respectfully traverse.

Tucker was filed June 7, 1995 and issued on October 7, 1997, after the filing date of this application (March 20, 1997). If the Examiner views Tucker as the only remaining prior art barrier to allowance of the present pending claims, applicants will claim priority from this patent, through a currently pending continuation application of the patent, which shares at least one inventor with the present application.

Rejections Under 35 U.S.C. § 102(b)

I

Claims 1, 7-9, 11-14 and 20-24 stand newly rejected as allegedly anticipated by Ammann. Specifically, the Examiner asserts that Ammann teaches the combination of collagen and CMC in osteogenic devices, said osteogenic device further comprising TCP and purified TGF-β. Office Action, ¶ 8, p. 8. Applicants respectfully traverse.

As discussed above, Ammann provides at best a general suggestion of combining a laundry list of carbohydrates and/or insoluble proteins. There are hundreds of possible combinations. Ammann does not specifically teach the

combination of collagen and CMC. In fact, Ammann's preferred carbohydrate is amylopectin.

In contrast, applicants particularly showed that collagen and CMC had synergistic results when used with osteogenic proteins. This particular combination is not taught in Ammann's general encyclopedic recitation.

II

Claims 20 and 22 stand newly rejected as allegedly anticipated by Beck (*J. Bone and Min. Res.* 6:1257-65, 1991). Specifically, the Examiner asserts that Beck teaches a composition comprising recombinant TGF-β1, and methycellulose, which is a device comprising a purified osteogenic protein capable of inducing repairs and a carrier, wherein said carrier comprises one part binding agent and zero parts matrix. Office Action, ¶ 9, p. 9. Applicants respectfully traverse.

Contrary to the Examiner's assertion, TGF-β does not fall within the definition of osteogenic protein in applicants' specification. The specification makes clear that TGF-β is not included as an osteogenic protein at p. 22, lines 3-7: "In addition to osteogenic proteins, various growth factors ... can also be contained within an improved osteogenic device. Thus various growth factors such as . . . TGF-β can be combined with an improved osteogenic device and delivered to a defect site" (emphasis added). Beck in no way anticipates the instant claims.

Rejections Under 35 U.S.C. § 103(a)

I

Claims 1, 32, 33, 35 and 36 remain rejected as allegedly obvious over Kuberasampath as applied to claim 1 above. Office Action, ¶ 5, p. 4. Applicants respectfully traverse the rejection.

As discussed above, Kuberasampath discloses using a synthetic collagen-GAG polymer as a matrix material. Kuberasampath does not teach or even suggest the use of any matrix material other than a synthetic polymer of collagen-GAG, much less the use of a matrix material that is not a synthetic polymer. Thus, the patent does not render claim 1 obvious.

For the same reasons, claims 32, 33, 35 and 36 are also non-obvious over the cited art.

II

Claims 1, 13 and 31 remain rejected as allegedly obvious over Kuberasampath as applied to claim 1 above, and further in view of Wozney (WO 95/24210) and Ammann (WO 94/15653). Specifically, the Examiner states that the rejected claims do not exclude the use of a synthetic polymer as a matrix, and thus applicants' arguments in their previous Response are not persuasive. Office Action, p. 5, lines 1-3.

Applicants respectfully disagree in light of Amendment 2. Kuberasampath's device includes a synthetic collagen-GAG polymer. In contrast, synthetic polymers are now more particularly excluded in amended base claim 1. Thus, Kuberasampath does not teach or suggest the device of amended claim 1. Neither Wozney nor Ammann remedies this deficiency, as discussed in applicants'

previous Response. Thus, a combination of these references would not have rendered obvious the device of claim 1 or dependent claim 13.

Furthermore, none of Kuberasampath, Wozney and Ammann teach or suggest the combined use of the particular ingredients recited in claim 31, i.e., OP-1, collagen matrix, and CMC. In fact, Exhibit 1 of applicants' previous Response teaches away the combined use of collagen and CMC.

The Examiner asserts that applicants' "teaching away" argument is not persuasive. Office Action, p. 5, line 17 through p. 6, line 8. Specifically, the Examiner states that in spite of the incompatibilities noted in Exhibit 1, both Tucker (United States Patent 5,674,292) and Ammann teach the combination of collagen and CMC in osteogenic devices. The Examiner further contends that Kuberasampath teaches mixtures of collagen and methycelluloses. According to the Examiner, the evidence of teaching away of Exhibit 1 does not outweigh the evidence of obviousness. Applicant respectfully traverse.

Tucker would be removed as prior art, as discussed above.

As to Ammann, it suggests the use of carbohydrates, insoluble protein, or a combination of "any of these" to bind TGF-β to tricalcium phosphate (TCP) (p. 10, lines 28-33). The carbohydrates enumerated in Ammann include agarose, cross-linked agarose, dextran, cross-linked dextran, inulin, hyaluronic acid, cellulose, cellulose derivatives such as CMC, and starch derivatives such as amylopectin. The insoluble proteins enumerated include gelatin, lyophilized gelatin, collagen and albumin. Thus, the general suggestion of combining "any of these" would yield a total

of hundreds of possible combinations. For instance, there will be 36 (9X4) different combinations of one enumerated carbohydrate and one enumerated insoluble protein; there will be at least 511 different combinations of any of the nine enumerated carbohydrate materials. Ammann does not teach that it has tested every single one of these hundreds of combinations and found them operable. Ammann's description is generic at best. Ammann does not provide any specific teaching on the particular combination of collagen and CMC out of the hundreds of possible combinations.[2] It provides no reasonable expectation that collagen and CMC can be combined to form a pharmaceutically acceptable carrier.

As to Kuberasampath, applicants again point out that what it describes is the use of cross-linked collagen and GAG as a matrix. This reference does not teach the use of pure, uncross-linked collagen as a matrix. In fact, its teaching implies that collagen is inferior than the collagen-GAG polymer as matrix material. The reference provides no way other than cross-linking with GAG to improve collagen's function as a matrix. Thus, the combined use of collagen (noncross-linked) with CMC would not have been obvious over Kuberasampath either.

The Examiner also states that applicants' arguments that a synergistic effect at low doses does not limit this advantage to exist only at low doses are not persuasive. The Examiner particularly contends that "the specification teaches that there were no marked differences in the histologic appearance between the standard

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2 It is also noted that this reference does not teach or suggest the combined use of the enumerated carbohydrates and insoluble proteins in the absence of TCP.

OP1 sites and the standard dose OP1/CMC sites" (Office Action, p. 6, lines 14-16). Applicants respectfully traverse.

Although there was no marked difference in histologic **appearance** between standard OP-1 sites and standard OP-1/CMC sites, other histologic criteria showed that standard OP-1/CMC sites had superior bone formation than standard OP-1 sites. The specification describes four histologic criteria that were used to measure the quality of new bone formation. They are quality of union, cortex development, residual implant material/internal architecture, and inflammatory response. See Table 6 at p. 68. Each of these criteria is graded on a scale of 0 to 4 according to histologic analysis.

The specification describes experiments showing that the standard dose OP-1/CMC device achieved the greatest mean histologic score/grade (12.08/16.0) as compared to other devices. See p. 85, lines 1-6. For example, the standard dose OP-1 sites had a corresponding score/grade of only 10.88/16.0. Thus, the histologic grading system clearly suggested that there was a marked difference between the standard OP-1 site and standard OP-1/CMC sites. Indeed, these and other related data led to the conclusion that "the improved devices unexpectedly achieved the greatest mean score and more frequently demonstrated continuous new bone with host bone" (p. 87, lines 6-7). The improvement is not limited to low doses of OP-1.

The Examiner has also argued that applicants' arguments that there is no motivation to combine the references are not persuasive. The Examiner asserts that it is *prima facie* obvious to combine methods each of which is taught by the prior art

to be useful for the same purpose, i.e. osteogenesis. Office Action, ¶ bridging pp. 6-7. Applicants respectfully traverse.

As already discussed above, Kuberasampath describes the use of cross-linked collagen and GAG as the matrix in an osteogenic device. Ammann teaches the use of polysaccharides (such as CMC) or insoluble protein (such as collagen) to bind TGF-beta to tricalcium phosphate (TCP) (p. 10, lines 28-33). However, this reference does not teach or suggest the combined use of CMC and collagen in the absence of TCP. The reference does not provide any expectation that a mixture of CMC and collagen alone, without TCP, would be a superior delivery system for TGF-beta, or OP-1, as recited in the claim. Furthermore, none of the above deficiencies of Kuberasampath and Ammann are remedied by Wozney, which was cited for teaching the combined use of particulate synthetic polymer such as polylactic acid/polyglycolic acid copolymer with a sequestering agent such as blood and CMC. Wozney does not suggest combining collagen with CMC. In fact, Wozney does mention using collagen as carrier for BMP, however, its very silence in combining collagen with a sequestering agent suggests that collagen need not be used in conjunction with a sequestering agent.

In conclusion, Kuberasampath, Ammann and Wozney, alone or in combination, do not provide a person of ordinary skill in the art with any teachings or motivation to arrive at an osteogenic device with the properties as recited in claims 1, 13 and 31.

III

Claims 1-5 and 31 stand newly rejected as allegedly obvious over

Ammann and Kuberasampath. Specifically, the Examiner asserts that Ammann teaches the combination of collagen and CMC in osteogenic devices at p. 10, lines 28-34; that the ratios of binding agent:matrix is disclosed in Ammann, although Ammann is silent with respect to recombinant OP-1. With respect to Kuberasampath, the Examiner asserts that Kuberasampath teaches the production of recombinant OP-1, which is in accordance with applicants' arguments that a recombinantly produced protein is an osteogenic protein "being not associated with other osteogenic proteins with which it is normally associated." The Examiner further suggests that although Kuberasampath is silent with respect to osteogenic devices comprising TGF-β, it would have been obvious to any skilled worker to modify the teachings of Ammann by making an osteogenic protein comprising OP-1, as taught by Kuberasampath. Applicants respectfully disagree.

As discussed earlier, Ammann and Kuberasampath, alone or in combination, do not teach or suggest the combined use of collagen and CMC with OP-1. For those reasons, the rejection should be withdrawn.

IV

Claims 1, 6, 15, 16, 32, 33, 35 and 36 stand newly rejected as allegedly obvious over Ammann and Ogawa (*J. Biol. Chem.* 267: 14233-7, 1992). Ammann is applied by the Examiner as discussed above. Ogawa is cited for teaching the synergistic effect of TGF-β and BMP and the use of saline as wetting agent in an osteogenic device. On this basis, the Examiner argues that it would have been obvious to any skilled worker to make an osteogenic device comprising TGF-β1, collagen and

CMC, as taught by Ammann, and to modify that teaching by making an osteogenic device comprising TGF-β and BMP, as taught by Ogawa, in order to achieve the synergistic effect of two different osteogenic proteins for more bone induction. Office Action, ¶ 12, pp. 11-13. Applicants respectfully disagree.

As discussed above, Ammann does not teach the particular combination of collagen and CMC. Neither does Ogawa, as admitted by the Examiner (Office Action, p. 12, lines 4-5). Thus, a combination of Ammann and Ogawa cannot possibly render obvious the claimed invention.[3]

V

Claims 17-19 and 25 stand newly rejected as allegedly obvious over Ammann and Cook (*Clin. Ortho. Rel. Res.* 301: 302-312, 1994) in view of Ogawa. Ammann is applied by the Examiner as discussed above. Ogawa is cited for teaching the use of saline in an osteogenic device. With regard to Cook, the Examiner argues that Cook's composition of bovine bone collagen and OP-1 "had the consistency of wet sand, which was spooned into the segmental defect site" and can be present at specific doses. The Examiner also contends that Cook teaches recombinant OP-1. On this basis, the Examiner alleges that it would have been obvious to make an osteogenic device comprising TGF-β1, collagen and CMC and to modify that teaching by using OP-1, as taught by Cook; and that it would have been obvious to any skilled worker to make an osteogenic device comprising OP-1, collagen and CMC, as taught by

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3 Also, as noted above, Ogawa and Ammann's TGF-β does not fall within the scope of osteogenic proteins in applicants' specification.

Ammann and Cook, and to modify that teaching by wetting the device with saline, as taught by Ogawa, in order to mold the osteogenic device into a shape suitable for implantation. Office Action, ¶ 13, pp. 13-15. Applicants respectfully disagree.

As discussed above, Ammann and Ogawa, alone or in combination, fails to teach the combined use of collagen and CMC with OP-1. This deficiency is not remedied by Cook.

CONCLUSION

For all the above reasons, applicants request that the Examiner withdraw all outstanding rejections and grant allowance to the pending claims.

Respectfully submitted,

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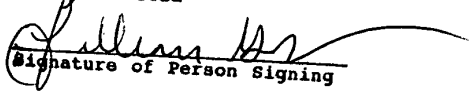

Signature of Person Signing

APPENDIX

1. (Six Times Amended) A device for inducing local bone or cartilage formation, comprising:

a purified osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects, said purified osteogenic protein being [not associated with other osteogenic proteins with which it is normally associated *in vivo*] isolated from naturally-occurring sources or produced by recombinant DNA techniques;

a matrix; [that does not comprise a synthetic polymer or demineralized bone;] and

a binding agent selected from the group consisting of mannitol, dextran, cellulose, white petrolatum, and derivatives thereof[.];

wherein the device does not comprise a synthetic polymer matrix or a demineralized bone matrix.

2. (Thrice Amended) The device of claim 1, wherein said osteogenic protein is selected from the group consisting of: OP1, OP2, OP3, BMP2, BMP3, BMP4, BMP5, BMP6, BMP9, BMP10, BMP11, BMP12, BMP15, BMP16, DPP, Vgl, 60A protein, GDF-1, GDF3, GDF5, GDF6, GDF7, GDF8, GDF9, GDF10, GDF11, and variants thereof having conservative amino acid substitutions and substantially similar osteogenic activity.

3. (Thrice Amended) The device of claim 1, wherein said osteogenic protein is selected from the group consisting of OP1, OP2, BMP2, BMP4, BMP5, BMP6, and variants thereof having conservative amino acid substitutions and substantially similar osteogenic activity.

4. (Twice Amended) The device of claim 1, wherein said osteogenic protein comprises an amino acid sequence having at least 70% homology with the C-terminal 102-106 amino acids, including the conserved seven cysteine domain, of human

[redacted]

OP1, said osteogenic protein capable of inducing repair of endochondral bone when implanted together with a matrix in a mammal.

5. The device of claim 1 wherein said osteogenic protein is OP-1.

6. The device of claim 1 wherein said device comprises at least two different osteogenic proteins.

7. (Amended) The device of claim 1, wherein said matrix is selected from the group consisting of: collagen, apatites, hydroxyapatites, tricalcium phosphates, and admixtures thereof.

8. The device of claim 1 wherein said matrix is collagen.

9. The device of claim 1 wherein said device comprises at least two different matrix materials.

11. The device of claim 1 wherein said binding agent is selected from the group consisting of alkylcelluloses.

12. The device of claim 1 wherein said binding agent is selected from the group consisting of methylcellulose, methylhydroxyethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, hydroxyalkylcelluloses, and admixtures thereof.

13. The device of claim 1 wherein said binding agent is carboxymethylcellulose or the sodium salt thereof.

14. The device of claim 1 wherein said device comprises at least two different binding agents.

15. The device of claim 1 further comprising a wetting agent.

16. The device of claim 15 wherein said wetting agent is saline.

17. (Three Times Amended) A device for inducing local bone or cartilage formation, comprising at least approximately 1.25 mg of purified OP-1 and at least approximately 180 mg of carboxymethylcellulose per 1000mg of collagen matrix, wherein said purified OP-1 is [not associated with other osteogenic proteins with which it is normally associated *in vivo*] isolated from naturally-occurring sources or produced by recombinant DNA techniques.

18. (Amended) The device of claim 17 comprising at least approximately 2.5 mg of OP-1 per 1000 mg of collagen matrix.

19. (Amended) The device of claim 17 or 18 comprising at least approximately 200 mg of carboxymethylcellulose per 1000 mg of collagen matrix.

20. (Five Times Amended) A device for inducing local cartilage or bone formation comprising a purified osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects and a carrier, wherein said carrier comprises one part binding agent and 10 or fewer parts (w/w) matrix, and said purified osteogenic protein is [not associated with other osteogenic proteins with which it is normally associated *in vivo*] isolated from naturally-occurring sources or produced by recombinant DNA techniques.

21. (Twice Amended) The device of claim 20 wherein said carrier comprises one part binding agent and 5 parts (w/w) matrix.

22. (Amended) The device of claim 20 wherein said carrier comprises fewer than 5 parts (w/w) matrix.

23. (Five Times Amended) A device for inducing local bone or cartilage formation comprising a purified osteogenic protein capable of inducing repair of endochondral bone, or cartilage, chondral, or osteochondral defects and a carrier, wherein said carrier comprises 10 or fewer parts (w/w) binding agent and 1 part matrix, and said purified osteogenic protein [is not associated with other osteogenic proteins with which it is normally associated *in vivo*] <u>being isolated from naturally-occurring sources or produced by recombinant DNA techniques</u>.

24. (Amended) The device of claim 23 wherein said carrier comprises fewer than 10 parts (w/w) binding agent.

25. The device of claim 17, 18 or 19 further comprising saline.

31. (Twice Amended) A device for inducing local bone or cartilage formation comprising:

purified OP-1;

collagen matrix; and

carboxymethylcellulose;

wherein said purified OP-1 is [not associated with other osteogenic proteins with which it is normally associated *in vivo*] <u>isolated from naturally-occurring sources or produced by recombinant DNA techniques</u>.

32. (Amended) A kit for inducing local bone or cartilage formation using the device of claim 1, the kit comprising:

(a) a receptacle adapted to house the osteogenic protein and the matrix material, and

(b) a receptacle adapted to house the binding agent,

wherein the osteogenic protein and matrix material are provided in the receptacle of part (a), and the binding agent is provided in the receptacle of part (b).

[redacted]

33. The kit of claim 32 further comprising a receptacle adapted to house a wetting agent.

35. (Amended) A kit for inducing local bone or cartilage formation using the device of claim 1, the kit comprising:

a first receptacle adapted to house the osteogenic protein, the matrix material, and the binding agent,

wherein the osteogenic protein, matrix material and binding agent are provided in said receptacle.

36. The kit of claim 35, further comprising a second receptacle adapted to house a wetting agent.